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Review Article

A REGULATORY PERSPECTIVE OF 505(b) (2) NEW DRUG APPLICATION

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ABSTRACT

USHavebeenconsideredprimary pharmaceuticalmarketintheworldsince longback.USpharmaceuticalmarketshares30to35% ofglobalpharmaceutical marketdespitelowgrowthrate inlasttwoyears.TremendousgrowthofUSpharma sectorisbasedonthreeprevailingfactorslikepresenceofbigpharma playersinthe county,governmentwillingnesstoprovide healthcarefacility andthirdlargest populationwith315million.Pharmacompanieshave threeways,NDA (NewDrug Application),ANDA(AbbreviatedNew DrugApplication)andOTC(Over The Counter)monograph,tomarkettheirdrugproductsinUS.NDA505(b) (2)isoneof thetypesof NDA. Section505(b)(2)wasintroducedinFD&CactthroughHatch-WaxmanAct1984andbecomingpopularday by dayduetoitsimportance.505(b)(2) applicationhaschangedtheconceptof new drugdefinition.505(b)(2) isstillunder its revolvingstageandFDAistakingallstepstokeepthings inlinewithout compromising to safety &efficacy which are utmost important from FDA perspective.FDAhasstartedemphasizingonaccess,affordabilityandqualityofdrug. ShortageofdrugisbeingaprobleminUSand 505(b)(2)applicationhascomein support ofFDA to solveit because it takes less timeto get through regulatory approvalprocess.505(b)(2)applicationmotivatesinnovationandatthesametime drugproduct pricedonotsurge highlike 505(b)(1)applicationduetoitslow requirementoffinanceindrugdevelopmentphase.Keepingaboveviewpointin mind,thisstudy encompassesdevelopmentof505(b)(2)applicationinthehistory of FDA,eligibility for505(b)(2)application,submissionrequirementsanddetailed CDER (Centerof DrugEvaluation and Research)reviewprocess ofNDA.

Keywords: US, 505(b) (2)NDA,FDA, Hatch-WaxmanAct 1984, CDER review process of NDA.

INTRODUCTION

FDA (Food and Drug Administration) isapharmaceuticalregulatory authority within theDepartment of Health and Human Services, one of the United States federal executive departments.

TheFDAisascientific,regulatory,andpublichealth agency thatoversees itemsaccountingfor25centsofevery dollarspentby consumers.Itsjurisdiction encompassesmostfoodproducts (otherthan meatand poultry), humanand animal drugs, therapeutic agentsofbiological origin, medical

devices, radiation-emitting products for consumer,medical, and occupationaluse, cosmetics, and animal feed[1].

Responsibility ofFDA

FDA is responsible for

- ✓ Protecting the public health by assuring that foods are safe, whole some, sanitary and properly labeled; human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective,
- ✓ Protecting the public from electronic product radiation,
- ✓ Assuring cosmetics and dietary supplements are safe and properly labeled,
- ✓ Regulating tobacco products,
- ✓ Advancing the public health by helping to speed product innovations,
- ✓ Helping the public get the accurate science-based information they need to use medicines, devices, and foods to improve their health.

FDA's responsibilities extend to the 50 United States, the District of Columbia, PuertoRico, Guam,the VirginIslands,American Samoa,andother U.S. territories andpossessions[2].

NDA505(b)(2)application is oneofthe applications through which applicant can launchthedrugproductinAmericaandindeedthisa pplicationdoesnotfallout ofthe scope of FDA and that is there as on why it is important to understand the organisation of FDA.

The FDA'sorganizationconsistsoftheOffice oftheCommissioner andfour directorates overseeing the core functions of the agency: Medical productsand tobacco, Foods, Global regulatoryoperations and policy, andOperations[3].

Understanding of 505(b)(2) application

Drugproductsthatmay besubmittedundersection505(b)(2)arenot completely newproducts,yetthey arenotgenerics.Thesemedicationshaveboth similaritiesandsomedifferencesfromaninnovator or branddrug. Forexample,a productmay havethesameactiveingredientasapreviouslyappr ovedproduct,but nowitisformulatedinadifferentdelivery mechanismorwithdifferentindications.

Thebasisforthe505(b)(2)applicationisthattherea lready isacertainamountof informationthatisknownabouttheactiveingredie nt.Assuch,repeatingallthe clinicalstudiesrequiredfora505(b)(1)application wouldbe expensiveandtime-consuming.So,undertherulesinsection505(b)(2), theapplicantcanrely on informationfromstudiesitdidnotconductandfor whichitdoesnothavethe rightof reference.

Applicationcan bes ubmitted as a 505(b)(2) application

1. Newchemical entity (NCE)/newmolecular entity (NME)

A505(b)(2)applicationmaybesubmittedforanNC Ewhensome partofthedatanecessary forapprovalisderivedfromstudiesnotconductedb y orfor theapplicantandtowhichtheapplicanthasnotobta inedarightof reference. ForanNCE, this data is likely to be derived from published studies, rather than FDA's previous finding of safety andeffectivenessofadrug. Ifthe applicant had a right of reference to all of the information necessary for approval,evenifthe applicanthadnotconducted the studies,the application would bea considered a505(b)(1)application.

2. Changes to previously approved drugs

Forchanges to a previously approved drug product ,an application mayrelyontheAgency'sfindingofsafetyandeffecti venessofthepreviouslyapprovedproduct,coupled withtheinformation neededtosupportthechange fromtheapprovedproduct.The additionalinformationcouldbenewstudies conductedbytheapplicantorpublisheddata.

Thisuseofsection505(b)(2), described in theregulations at 21 CFR 314.54, was intended to encourage innovationwithoutcreatingduplicateworkandrefl ectsthesameprincipleas the505(j)application:itiswastefulandunnecessar ytocarry outstudiesto demonstrate what is alreadyknownabout a drug.

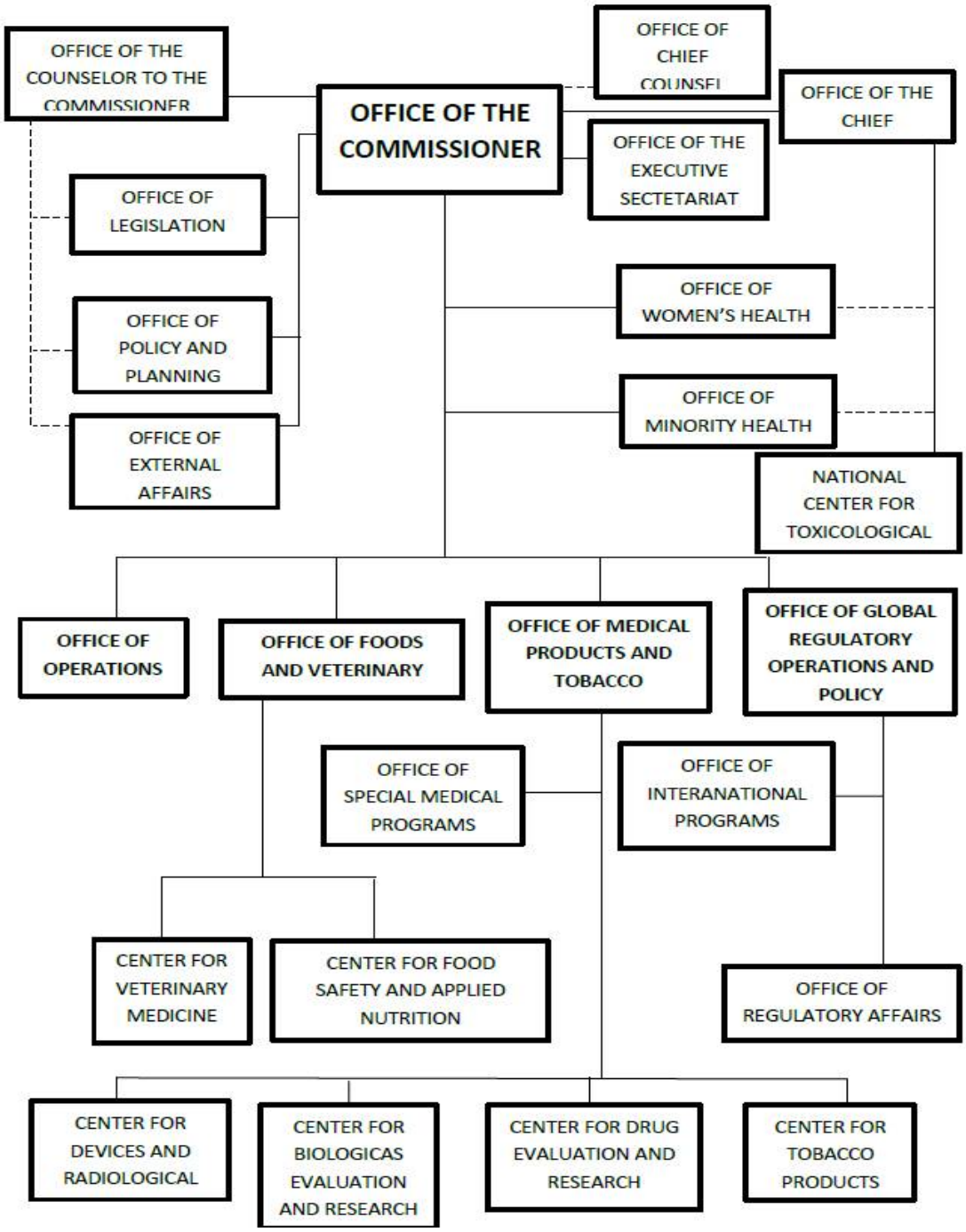
Inaddition,anapplicantmay submita505(b)(2)applicationfora change in a drug product that is eligible for consideration pursuant to a suitabilitypetitionunderSection505(j)(2)(C)ofth eAct. Inthepreambletothe implementingregulationsfor theHatch-WaxmanamendmentstotheAct,the Agency notedthatanapplicationsubmittedpursuanttosec tion505(b)(2)ofthe Actisappropriate evenwhenitcouldalsobesubmittedinaccordance witha suitabilitypetition as defined at section 505(j)(2)(C) of the Act.

DISCUSSION

5.1.2 Organisation of FDA

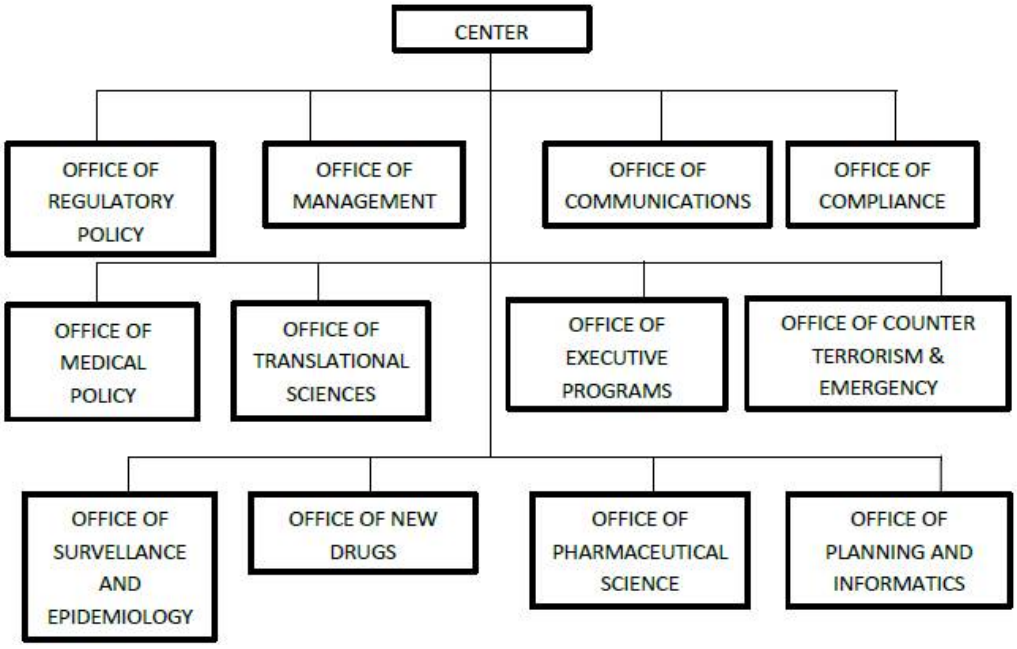
FDA's organization consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency and these four offices are listed out as below and sub branches of these offices and office of the Commissioner aredepicted in the figure 2.

Figure 2: Structure of FDA Organisation[17]



TheFDA"sCenterforCDERpromotesandprotectst hehealthofAmericans by assuring that all prescription and over-the-counter drugs are safe and effective. CDER evaluates all new drugs before they are sold,and serves as a consumer watchdogforthemorethan10,000drugsonthemar ketto be sure they continue to meet the highest standards. The center routinely monitors TV, radio, and print drug ads to ensure they are truthful and balanced. CDER also plays a critical role in providing health professionals and consumers information to use drugs appropriately and safely.

Figure 3: Structure of CDER[18]



5.4 ORIGIN OF 505(b)(2)APPLICATION

Inthehypotheticalexample(Figure4)DEF is the innovator company. It hasinnovatedadrugproductcontainingXYZactivei ngredientandthedosage form (DF) of the drugproductistablet.Brandname ofthe drugproductisABCandactive ingredientXYZisNCE(NewChemicalEntity). This XYZ possess a very good pharmacological action and it treats the disease well. Now the question is that XYZ is active in the form of tablet only or activeness of XYZ lies in the nature of XYZ? It is not a brain-teaser and answer is very obvious that activeness of XYZ is because of its nature. It is the tablet dosage form that conveys XYZ to the body system to treat the undesired pathological condition of the body. But it never means XYZ would not be effective in dosage form other than tablet.

It would also wrong to say thatXYZwillnotbeactiveincombinationwith other activeingredient. Otherpossibilityis also veryinteresting to notethatdoes XYZ possessthepotentialto theextentofitsuseundertheknownindicationslist edunder theapprovedlabel?The factisthatindicationsofXYZaremade onthebasisofthe resultsobtainedattheendof the clinicaltrials.Clinicaltrialsareconducted onthe basisofthepreliminaryfindingsattheearly stageofdrugdevelopment.Approach adoptedintheearly stageofdrugdevelopmentisnotalwaysbroadrathe ritisvery specific. Anditisoftenobservedsuch product wouldfindnewindicationsduringits lifecycle.

Bunchofotherpossibilitieswaitaheadonthewayan deach possibility is practicallyobservedinthehistory.Inabovecases,a napplicant,proposingtodevelop anewdrugproductaftermakingsuitablemodificati onsinexistingversionofnew drugproduct,hastoholdonhisideatillallpatentsget clearrelatedtoexistingnew drug product. This stateof affairs produced the need of 505(b)(2)application.

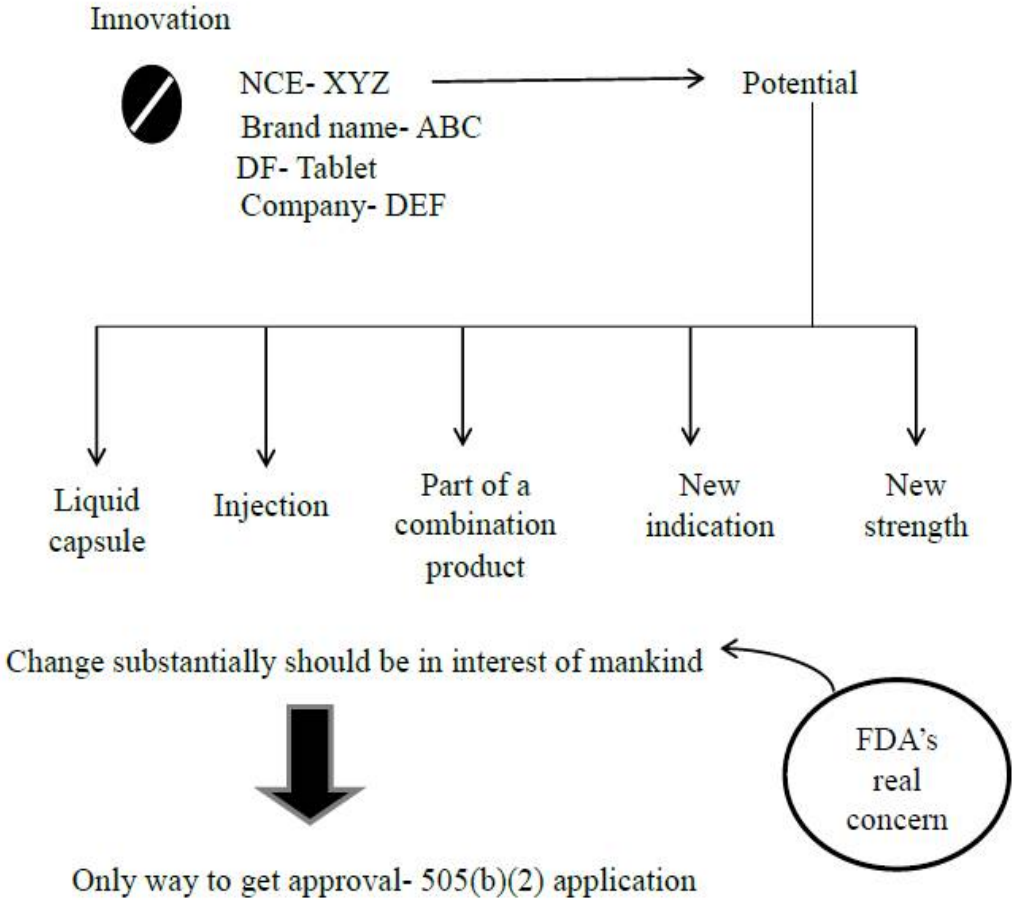


Fig. 4: An hypothetical exampleto explain theneed forthe505(b)(2)application

5.5.3 Applicationcan'tbesubmittedas 505(b)(2)applications

- ✓ Anapplicationthatisaduplicateof a listeddrugandeligiblefor approval under section 505(j)(see21 CFR 314.101(d) (9)); or
- ✓ Anapplicationinwhichtheonlydifference fromthereferencelisteddrug isthattheextenttowhichtheactive ingredient(s)isabsorbedor otherwise madeavailabletothesiteofactionisless thanthelisteddrug(21CFR 314.54(b)(1)); or
- ✓ Anapplicationinwhichtheonlydifference fromthereferencelisteddrug isthattherateatwhichitsactiveingredient(s)isabsorbedorotherwise madeavailabletothesiteofactionisunintentionally lessthanthatofthe listed drug (21 CFR 314.54(b)(2).

Summary of Milestones for the Full Review Cycle

The followingtable summarizesthe milestonesthroughoutthereview cycle.

Table 3: Summary of milestones throughout the review cycle

	Standard Review			**PriorityReview**		
	ODE Signatory	ODE Signatory	ODE Signatory PDUFAV Program	ODE Signatory	DD Signatory	ODE Signatory PDUFAV Program
MilestonesforSteps 2 and3:FilingDetermination andReviewPlanning						
1. ApplicationReceipt (2.1)	Day0					
2. AssignRPM(2.1)BeginRegulatory Filing Review	Days0-14					
3. Acknowledge applicationreceipt in writing (2.4)	ByDay14					
4. AssignReviewTeamSchedulefilingand planningmeetings	ByDay14					
5. DetermineSignatoryAuthority (3.1.1), CDTL (3.1.2),and preliminaryPriority/ Standard reviewdesignation(3.1.3)	ByDay14					
6. HoldBIMOsiteselectionmeeting	Byday38 (day23 forpriority)					
7. HoldApplicant Orientation Presentation(optional)(3.1.6)	ByDay45 (byday30 forpriority)					
8. Conduct filingreview, request standard Consults, identifyInspectionactions, conveypotentialRTF issuestoApplicant (3.2.1)	ByDay45 (byday30 forpriority)					
9. Holdfiling meetingto makefiling decision (3.2.3)	ByDay 45	ByDay 45	ByDay 45	ByDay 30	ByDay 30	ByDay 30
10. Holdplanning meetingtoplanthe review(3.3)	ByDay 45	ByDay 45	ByDay 45	ByDay 30	ByDay 30	ByDay 30
11. InformApplicantof aPriority DesignationinWritingCommunicate Filing Determination toApplicant (fors and priorityNDAs)NotifyApplicant of a Refuse-to-Filedetermination(3.2.3)	ByDay60					
12. CommunicateFilingReviewIssues (3.2.2)	ByDay74					
13. Communicate"Program" Review Timelineto Applicant (3.3)(ifapplicable)	-----	-----	ByDay 74	-----	-----	ByDay 74
MilestonesforStepFour:Conduct Review						
14. Conduct Review(4)	Month 1.5-8.0	Month 1.5-8.75	Month 1.5-8.0	Month 1.0-5.0	Month 1.0-5.25	Month 1.0-5.0
15. Ifapplicable, discusssafetyfindings with OSE (re:REMS, PMRs)and OC-OSI (re: REMS)	Before theMid-CycleMeeting ataregularlyscheduled Review Team Meeting					
16. HoldMid-CycleMeeting(4.4)	Month 5.0	Month 5.0	Month 5.0	Month 3.0	Month 3.0	Month 3.0
17. Post-Mid-CycleMeeting Communicationwith Applicant(4.5)	-----	-----	Month 5.5	-----	-----	Month 3.5
18. CompletePrimaryReviews,including Secondary ReviewSign-Off(4.9)	Month 8.0	Month 8.75	Month 8.0	Month 5.0	Month 5.25	Month 5.0

19. CompleteSecondaryReview (when needed)(4.9)	Month 8.25	Month 9.0	Month 8.25	Month 5.1	Month 5.25	Month 5.1
20. IssueDisciplineReviewLetters (4.10)	-----	-----	1week after primary review	-----	-----	3days after primary review
21. HoldWrap-UpMeeting, including SafetyDiscussion (4.16)	8wkspriorto PDUFA goal date	5wkspriorto PDUFA goal date	7wkspriorto PDUFA goal date	4wkspriorto PDUFA goal date	2wks prior to PDUFA goal date	5wkspriorto PDUFA goal date
22. CompleteCDTL Memo(4.17)	6wkspriorto PDUFA goal date	3wkspriorto PDUFA goal date	6wkspriorto PDUFA goal date	3wkspriorto PDUFA goal date	2wks prior to PDUFA goal date	4wkspriorto PDUFA goal date
MilestonesforLabeling, PMRs/PMCs, REMS						
23. Ifindicated, send REMSNotification Letterto Applicant (REMSmemomust be completed)(4.5)	Within6weeks afterMid-CycleMeeting					
24. BeginREMS Discussionswith Applicant(if not alreadystarted)(4.8.2)	ByMonth 6 (orwithin2 weeksafterREMSnotificationletteris issued)					
25. ReviewTeamDraftsLabeling, PMC, PMR(4.8.1)	Month 5.5–7.0	Month 5.5–7.0	Month 5.5–7.0	Month 3.5–4.5	Month 3.5–4.5	Month 3.5–4.5
26. SendLabeling/PMR/PMC toApplicant (4.8.1)	Month 8.25	Month 9.0	Month 8.25	Month 5.0	Month 5.25	Month 5.0
27. Labeling/PMR/PMC Discussionswith Applicant Begin(4.8.1)	Month 8.5	Month 9.25	Month 8.5	Month 5.25	Month 5.5	Month 5.25
MilestonesforLate-CycleMeeting						
28. HoldPre-MeetingforLate-Cycle Meeting(4.12)	-----	-----	Month 8.0	-----	-----	Month 5.25
29. Send Agency Late-CycleMeeting BriefingPackagetoApplicant (4.13)	-----	-----	By20 days before AC Meeting or12 days before Late Cycle Mtgifno	-----	-----	By20 days before AC Meeting or12 days before Late Cycle Mtgif
			ACMtg			noAC Mtg
30. HoldLate-CycleMeetingwith Applicant(4.13)	-----	-----	12 days before AC Meeting orby Month 9.0if no ACMtg	-----	-----	12 days before AC Meeting orby Month 6.0if no ACMtg
MilestonesforACMeeting						
31. Plan ACMeeting(4.7.1)	Beginwhen need forACmeetingisidentified					
32. Send draft questionsforACto DFO (4.7.1)	12weeks priortomeeting					

33. Disseminateand discloseapplicant andbackgroundmaterials (4.7.1)	4weeks prior tomeeting					
34. Holdinternal practicemeetingsto prepare for ACmeeting(4.7.1)	2-6 weeks priorto meeting	2-6 weeks priorto meeting	2 weeks prior to meeting	2-6 weeks priorto meeting	-----	2 weeks prior to meeting
35. Submit final questionsforACto applicant(4.7.1)	-----	-----	2days before AC Meeting	-----	-----	2days before AC Meeting
36. Conduct ACMeeting(4.7.1)	Month 7.0-8.0		By Month 9.0	Month 4.0-5.0		By Month 6.0
37. Holdinternal post-ACmeeting (4.7.1)	Within2weeks afterACmeeting					
38. Confidential memotoACtoannounce action andinterpretationof ACinput (4.7.1)	Within30 daysof taking action					
MilestonesforStep5:TakeAction						
39. HoldPeRCmeeting	4-6 weeks priortoaction					
40. CompileandCirculateActionLetter and ActionPackage(5.2)	6weeks priorto action	3weeks priorto action	6weeks priorto action	3weeks priorto action	2 weeks prior to action	3weeks priorto action
41. DivisionDirectorReviewofAction Packageand Decision (5.1)	3-6 weeks priorto action	0-3 weeks priorto action	6weeks priorto action	1.5-3 weeks priorto action	0-2 weeks prior to action	1.5-3 weeks priorto action
42. REMSfinalized;DRISK reviewof REMS finalized (5.2)	1-2 weeks priortoaction					
43. ODEReviewof ActionPackageand Decision (5.1)	0-3 weeks priorto action	-----	0-3 weeks priorto action	0-1.5 weeks priorto action	-----	0-1.5 weeks priorto action
44. OCclearanceof confirmatoryTB-EER (sonly)	At least 30daysbeforeApproval Action					
45. IssueAction Letter(5.2)	Month 10.0	Month 10.0	Month 12.0	Month 6.0	Month 6.0	Month 8.0

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